(1) Obj ction to th Declaration

The Examiner has objected to the previously submitted Declaration (filed October 9, 1996), as not complying with the requirements of 37 C.F.R. 1.63(c) and has required the submission of a new Declaration. The Examiner has stated on page 1 of the Office Action that Applicants' Declaration does not acknowledge the filing of any foreign application. Applicants respectfully refer the Examiner to page 1 of the previously submitted Declaration wherein Applicants properly claimed foreign priority pursuant to 37 C.F.R. 1.55. Applicants submit that their Declaration clearly identifies the foreign application FR94/03191 which was filed in France on March 18, 1994 and to which foreign priority under 35 U.S.C. §119 is claimed.

Applicants are currently preparing a new Declaration which identifies additional applications to which Applicants claim priority under 35 U.S.C. §§§ 119, 120, and 365. Applicants submit herewith an unsigned copy of this new Declaration which identifies these prior applications. Applicants will submit the signed original Declaration as soon as all Inventors' signatures have been obtained.

(2) Rejection of Claims 27-29, 31-34, 37-41, and 48-50 Under Section 112, First Paragraph

Claims 27-29, 31-34, 37-41, and 48-50 stand rejected under 35 U.S.C. § 112, first paragraph. Applicants have canceled claims 29 and 39 without prejudice and have amended claims 27, 28, 31-34, 37, 38, 40, 41, and 48-50. Claims 27, 28, 31-34, 37, 38, 40, 41, and 48-50 are pending in the instant amendment. Applicants respectfully traverse this rejection with respect to the remaining claims. Applicants submit that the claimed invention is enabled under Section 112, first paragraph. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

<u>The Specification enables BDNF:</u>

On page 2 of the Office Action, the Examiner has stated that Applicants' Specification is enabling for a cDNA encoding BDNF (or a precursor protein) that is adequately characterized by chemical or structural characteristics. Applicants agree with the Examiner and submit that their Specification enables a cDNA encoding BDNF or a precursor BDNF protein.

Indeed, Applicants' Specification clearly describes brain-derived neurotrophic factor (BDNF) as an identified protein of 118 amino acids and a molecular weight of

13.5 kD which functions as a neurotrophic factor and adenoviruses comprising a cDNA encoding BDNF and how to make adenoviruses comprising a cDNA encoding BDNF wherein the BDNF protein is expressed in a cell of the central nervous system (see page 2, lines 13-24, page 4, line 24 to page 5, line 2, page 7, line 14 to page 11, line 26, and Examples 1-7). Applicants also disclose that the cDNA sequence of the adenoviruses of the present invention may encode the proBDNF protein or the preproBDNF protein (page 6, lines 17-20 and page 7, line 19-21 of the Specification). Applicants describe how to use the adenoviruses and infected mammalian cells of the invention on page 11, line 27 to page 17, line 25 and within Examples 3 and 5-7 to transfer BDNF protein expression.

Applicants have amended independent claim 27 to recite a replication defective recombinant adenovirus comprising a cDNA encoding brain-derived neurotrophic factor (BDNF), wherein the adenovirus E1 gene is non-functional, and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system. Applicants have also amended independent claim 37 in the instant amendment to recite a replication defective recombinant adenovirus comprising a cDNA encoding human brain-derived neurotrophic factor (hBDNF) operably linked to a promoter controlling expression in a nerve cell, wherein the adenovirus E1 gene is non-functional. Applicants submit that amended claims 27 and 37 and their dependent claims 28, 31-34, 38, 40, 41, and 48-50 are enabled.

The Examiner contends that the Specification does not reasonably provide enablement for <u>any substance or derivative</u> that may be named "brain-derived neurotrophic factor" (see page 2, Office Action). Contrary to the Examiner's assertion, Applicants' amended claims are not directed to "any substance or derivative" (see the Office action at page 2), but are directed to replication defective recombinant adenoviruses comprising <u>a cDNA encoding brain-derived neurotrophic factor (BDNF)</u> and mammalian cells infected with the adenoviruses of the invention. In addition, Applicants respectfully submit that one of ordinary skill in the art is fully enabled by the term "brain-derived neurotrophic factor" for a molecule that has the chemical and structural characteristics to function as BDNF, *e.g.*, as described in Barde *et al.* (US Patent 5,180,820) and EXHIBITS "A-D" (submitted herewith).

As evidence that the term "brain-derived neurotrophic factor" is well known in the art to represent a specific neurotrophic factor, Applicants submit herewith EXHIBITS "A-D". EXHIBIT "A" (Rosenthal *et al.*, 1991.) describes the primary structure of a human precursor BDNF cDNA, the biological activities of purified human BDNF protein, and the tissue distribution of rat BDNF (Abstract and Figures

1-3). EXHIBIT "B" (Isackson *et al.*, 1991.) provides the cloned cDNA coding sequences of the mature region of BDNF from monkey, rat, chicken, and *Xenopus* genomic DNA. EXHIBIT "B" demonstrates that the predicted amino acid sequences of monkey and rat BDNF are identical to other mammalian BDNF sequences (Abstract and Figure 1). In addition, EXHIBIT "B" teaches that the amino acid sequences of porcine, mouse, rat, and human mature BDNF protein are identical (see page 260, second column, second paragraph). EXHIBITS "C" (Maisonpierre *et al.*, 1991.) and "D" (Ozcelik *et al.*, 1991.) identify the chromosomal location of the BDNF gene in the human, rat, and mouse genomes. In addition, EXHIBIT "C" also provides the molecular cloning of the human and rat genes encoding BDNF and the demonstration that the mature form of BDNF is identical in all mammals examined.

Based upon the evidence presented in EXHIBITS "A-D", Applicants respectfully submit that one of ordinary skill in the art would recognize that the terms "brain-derived neurotrophic factor" and "BDNF" represent a specific neurotrophic factor which is characterized by specific chemical and structural characteristics known in the art. Furthermore, the submitted EXHIBITS "A-D" are evidence that the BDNF encoding nucleic acids and BDNF protein exist and were known in the art at the time Applicants' application was filed. Applicants respectfully remind the Examiner that the Federal Circuit court has ruled that a patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent Inc.* 3 USPQ2d 1737 (Fed. Cir. 1987). Therefore, Applicants submit that the description of the invention and the Examples present in the Specification enable one of ordinary skill in art to make the invention as claimed.

Specifically, Applicants believe that their Specification clearly teaches one skilled in the art how to make replication defective recombinant adenoviruses comprising a cDNA encoding brain-derived neurotrophic factor (BDNF), wherein the adenovirus E1 gene is non-functional, and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system, the subject matter of claims 27, 28, 31-34, 37, 38, 40, and 41, and mammalian cells infected with such replication defective recombinant adenoviruses, the subject matter of claims 48-50, and how to use these adenoviruses and adenoviral infected mammalian cells to express BDNF protein. Accordingly, the Specification clearly meets the enablement requirements of 35 U.S.C. § 112, first paragraph.

In conclusion, the Examiner has not met the burden of establishing non-enablement of the claimed invention, and the evidence of record would rebut any

such determination if properly made out. The MPEP is clear on the burden placed on the Examiner to support a rejection for lack of enablement.

> In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. (MPEP 2164.04)
>
> Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. (MPEP 2164)
>
> In making the determination of enablement, the Examiner shall consider the original disclosure and all evidence in the record, weighing evidence that supports enablement against evidence that the specification is not enabling. (MPEP 2164.05)

The Examiner has not provided any credible scientific evidence, including an Affidavit of personal knowledge under 37 C.F.R. § 1.107(b) to support this rejection, as required. See MPEP 2164 et seq. Thus, the Examiner has not met the burden of showing lack of enablement. Moreover, even if the Examiner had met this burden, the evidence of record in this application in favor of enablement of the claimed methods far outweighs the evidence provided by the Examiner.

Applicants submit respectfully that the Specification contains a detailed description of how to make a replication defective recombinant adenovirus comprising a cDNA encoding brain-derived neurotrophic factor (BDNF), wherein the adenovirus E1 gene is non-functional, and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system and a mammalian cell infected with an adenovirus of the invention and that the examples present in the application comprise compelling evidence of how to use these viruses and infected mammalian cells for BDNF gene transfer and protein expression. Accordingly, Applicants' Specification meets the requirements of 35 U.S.C. § 112, first paragraph. Therefore, Applicants submit that claims 27, 28, 31-34, 37, 38, 40, 41, and 48-50 are enabled and request respectfully that the rejection be reconsidered and withdrawn.

(3) Rejection of Claims 27-29, 31-35, 37-41, and 48-50 Under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Le Gal La Salle *et al.*

Claims 27-29, 31-35, 37-41, and 48-50 stand rejected under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Le Gal La Salle *et al.* Applicants have canceled claims 29 and 39 without prejudice in the instant amendment. Applicants have amended the remaining pending claims 27, 28, 31-35, 37, 38, 40, 41, and 48-50 in the instant amendment. Applicants respectfully traverse this rejection with respect to the remaining claims. The combination of references in no way teaches or suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Barde *et al.*

Barde *et al.* teach nucleic acid sequences encoding porcine and human brain derived neurotrophic factor (BDNF) and the substantially pure BDNF protein, peptide fragments, or derivatives produced in quantity from these nucleic acid sequences (Figures 1 and 5). This reference also teaches antibodies directed toward the BDNF protein, peptide fragments, or derivatives. Barde *et al.* are concerned with producing sufficient quantities of BDNF to enable anti-BDNF antibody production and to support diagnostic and therapeutic applications of BDNF protein (see column 10, lines 42-52 and columns 25-28).

Le Gal La Salle *et al.*

The Le Gal La Salle *et al.* reference was published in Science in 1993. In the previous reply mailed August 18, 1998, Applicants set forth that the subject matter of the instant application is entitled to priority under 35 U.S.C. §§§ 119, 120, and 365 of co-pending US Application Serial No. 08/403,868, filed April 28, 1995, which is the National Phase of PCT/EP93/02519, filed September 17, 1993, and of European Patent Application No. EP92-402644.6, filed September 25, 1992. Thus, the instant application is effectively a continuation-in-part of the above-noted priority applications. Thus, with an effective US filing date of September 1993, and a priority date of September 1992, Le Gal La Salle *et al.*, 1993 is not available as prior art to the instant application.

Applicants are in the process of obtaining a certified copy of the European Patent Application No. EP92-402644.6, which was filed on September 25, 1992. Applicants will submit this certified copy as soon as it is available. A copy of the EP92-402644.6 priority document is submitted herewith for the Examiner's consideration.

(b) Barde *et al.* Do Not Render Obvious Applicants' Claimed Invention

Applicants' independent claims 27 and 37 have been amended in the instant amendment and relate to replication defective recombinant adenoviruses comprising a cDNA encoding BDNF (claim 27) or human BDNF (hBDNF, claim 37), wherein the adenovirus E1 gene is non-functional, and wherein the BDNF or hBDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system. The reference cited by the Examiner does not teach or suggest the invention defined by claims 27, 37, or any of the claims dependent thereon. The Barde *et al.* reference is deficient because it:

(1) fails to disclose a replication defective recombinant adenovirus comprising a cDNA encoding BDNF;
(2) fails to disclose a promoter which controls expression in a cell of the central nervous system;
(3) fails to enable adenoviral gene delivery of BDNF encoding cDNA to a cell of the central nervous system as observed by Applicants; and
(4) fails to disclose a mammalian cell infected with a replication defective recombinant adenovirus comprising a cDNA encoding BDNF.

Barde *et al.* fail to teach or suggest a replication defective recombinant adenovirus vector, particularly a vector with a non-functional E1 region. Specifically, Barde *et al.* fail to teach or suggest a replication defective recombinant adenovirus comprising a cDNA encoding BDNF, wherein the adenovirus E1 gene is non-functional and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system. These authors certainly do not teach mammalian cells infected with such a replication defective adenovirus. Absent such a disclosure, Barde *et al.* cannot possibly render *prima*

facie obvious the invention defined by Applicants' independent claims 27 and 37, or the claims dependent thereon.

(c) La Gal La Salle *et al.* do not correct the deficiencies of Barde *et al.*

As discussed above, Barde *et al.* do not teach or suggest the claimed invention. Based upon Applicants' claimed priority date of September 1992, the Le Gal La Salle *et al.*, 1993 reference is not available as prior art to the instant application. Accordingly, La Gal La Salle *et al.* cannot possibly correct the deficiencies of Barde *et al.* Applicants respectfully request that this rejection be reconsidered and withdrawn.

(4) Rejection of Claims 27-29, 31-35, 37-41, and 48-50 Under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Wilson *et al.*

Claims 27-29, 31-35, 37-41, and 48-50 stand rejected under Section 103(a) as being allegedly unpatentable over Barde *et al.* in view of Wilson *et al.* (US patent 5,585,362). Applicants have canceled claims 29 and 39 without prejudice and have amended claims 27, 28, 31-35, 37, 38, 40, 41, and 48-50 in the instant amendment. Claims 27, 28, 31-35, 37, 38, 40, 41, and 48-50 are pending in the instant application. Applicants respectfully traverse this rejection with respect to the remaining claims. The combination of references in no way teaches or suggests Applicants' invention and, therefore, fails to establish a *prima facie* case of obviousness. Accordingly, Applicants request respectfully that the rejection be reconsidered and withdrawn.

(a) Discussion of the cited references

Barde *et al.*

As discussed above in Section 3, Barde *et al.* do not teach or suggest the claimed invention. In particular, Barde *et al.* do not suggest replication defective recombinant adenoviruses comprising a cDNA encoding BDNF, wherein the adenovirus E1 gene is non-functional, and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system. Barde *et al.* certainly do not suggest mammalian cells infected with such a replication defective adenovirus of the claimed invention.

Wilson *et al.*

The subject matter which the Examiner has relied upon in Wilson *et al.* (US Patent 5,585,362 issued December 17, 1996) has an effective US filing date of June 7, 1993. In the previous reply mailed August 18, 1998, Applicants set forth that the subject matter of the instant application is entitled to priority under 35 U.S.C. §§§ 119, 120, and 365 of co-pending US Application Serial No. 08/403,868, filed April 28, 1995, which is the National Phase of PCT/EP93/02519, filed September 17, 1993, and of European Patent Application No. EP92-402644.6, filed September 25, 1992. Thus, the instant application is effectively a continuation-in-part of the above-noted priority applications. Thus, with an effective US filing date of September 1993, and a priority date of September 1992, the Wilson *et al.* (effective filing date of June 7, 1993) is not available as prior art to the instant application.

On page 4 of the Office Action, the Examiner contends that the effective US filing date of the Wilson *et al.* US 5,585,362 reference is September 11, 1992. Applicants respectfully disagree and submit that the Examiner has erroneously relied upon the disclosure of abandoned application Serial number 943,952 (see "Related U.S. Application Data" section on page 1 of Wilson *et al.*). To demonstrate that the subject matter which the Examiner has relied upon in Wilson *et al.* has an effective US filing date of June 7, 1993., Applicants submit herewith EXHIBITS "E" and "F" as evidence of the disclosures contained within the priority applications of Wilson *et al.*

Wilson *et al.* (US 5,585,362) is a continuation-in-part of Serial number 943,952, filed September 11, 1992, which was abandoned. EXHIBIT "E" (US Patent 5,625,128) is a continuation of this same Serial number 943,952 and its disclosure must be considered the same as that of the abandoned 943,952 application. The disclosure of EXHBIT "E" relates to non-human animal models of a human airway. EXHIBIT "E" does not disclose adenovirus vectors for gene therapy.

Wilson *et al.* (US 5,585,362) is also a continuation-in-part of Serial number 67,296, filed May 25, 1993, and now abandoned, which was a division of Serial number 584,275, filed September 18, 1990, now US Patent 5,240,846. Applicants submit herewith EXHIBIT "F" which is US Patent 5,240,846. The disclosure of EXHIBIT "F", as a divisional application, must be considered the same as that of the abandoned 67,296 application. The disclosure of EXHBIT "F" relates to gene therapy for cystic fibrosis through delivery and expression of a functional CFTR gene to cells of a CF patient. EXHIBIT "F" does not disclose adenovirus vectors for gene therapy. Applicants submit that EXHIBITS "E" and "F" are evidenc that the subject matter of Wilson *et al.* (US 5,585,362) that the Examiner has relied upon as

ground for the present rejection is not disclosed within the 943,952 or 67,296 applications. Accordingly, this subject matter of Wilson *et al.* (US 5,585,362) is not entitled to the filing date of the 943,952 application (September 11, 1992), the filing date of the 67,296 application (May 25, 1993), or the filing date of the 584,275 application (September 18, 1990). Thus, the subject matter added by Wilson *et al.*'s continuation-in-part application is entitled to an effective filing date of June 7, 1993[i]. For this reason, the subject matter cited by the Examiner is not available as prior art to the instant application with a claim of priority to September 25, 1992.

Applicants are in the process of obtaining a certified copy of the European Patent Application No. EP92-402644.6, which was filed on September 25, 1992. Applicants will submit this certified copy as soon as it is available. A copy of the EP92-402644.6 priority document is submitted herewith for the Examiner's consideration.

(b) Barde *et al.* Do Not Render Obvious the Invention of Claims

As discussed above in Section 3, Barde *et al.* do not teach or suggest the claimed invention. Barde *et al.* fail to teach or suggest a replication defective recombinant adenovirus vector, particularly a vector with a non-functional E1 region. Specifically, Barde *et al.* fail to teach or suggest a replication defective recombinant adenovirus comprising a cDNA encoding BDNF, wherein the adenovirus E1 gene is non-functional and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system. These authors certainly do not teach mammalian cells infected with such a replication defective adenovirus. Absent such a disclosure, Barde *et al.* cannot possibly render *prima facie* obvious the invention defined by Applicants' independent claims 27 and 37, or the claims dependent thereon.

(c) Wilson *et al.* do not correct the deficiencies of Barde *et al.*

As discussed above, Barde *et al.* do not teach or suggest the claimed invention. Based upon Applicants' claimed priority date of September 1992, the Wilson *et al.* US patent reference (effective US filing date of June 7, 1993) is not available as prior art to the instant application. Accordingly, Wilson *et al.* cannot possibly correct the deficiencies of Barde *et al.* Applicants respectfully request that this rejection be reconsidered and withdrawn.

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[i] Applicants have ordered the complete file history of Wilson *et al.* (US 5,585,362) including priority

Applicants note that claims 42-47 are not rejected over prior art. Applicants agree with the Examiner that the prior art of record neither anticipates nor renders obvious the claimed invention. Thus, by amending the claims to more particularly point out and distinctly claim that which Applicants regard as their invention, in accordance with the teachings of the Specification, Applicants have clarified the novelty and non-obviousness of the invention identified by the Examiner in claims 42-47. All of the claims are therefore free over the art of record.

Conclusion

In view of the foregoing amendments and remarks, Applicants believe that this application is in condition for allowance. Favorable reconsideration and an action passing this case to issue are therefore requested respectfully. If a telephone interview would be of assistance in advancing prosecution of this application, Applicants invite the Examiner to contact their attorney, Ross J. Oehler, at (610) 454-3883.

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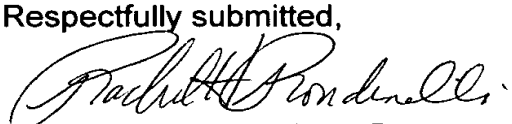
Respectfully submitted,



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documents to verify this date. Applicants intend to file a supplemental reply confirming this date.

APPENDIX
U.S. Patent Application Serial No. 08/716,209
" Recombinant Adenoviruses Coding For Brain-Derived Neurotrophic Factor (BDNF)"
RPR File No. ST94014-US
Pending Claims

27. (Twice Amended) A replication defective recombinant adenovirus comprising a cDNA encoding brain-derived neurotrophic factor (BDNF), wherein the adenovirus E1 gene is non-functional, and wherein the BDNF encoding cDNA is operably linked to a signal controlling expression in a cell of the central nervous system.

28. (Twice Amended) The replication defective recombinant adenovirus according to Claim 27, wherein the cDNA encodes prepro-BDNF.

31. (Twice Amended) The replication defective recombinant adenovirus according to Claim 27, wherein the cDNA encodes human prepro-BDNF.

32. (Twice Amended) The replication defective recombinant adenovirus according to Claim 27, wherein the cDNA is operably linked to a signal controlling expression in a nerve cell.

33. (Twice Amended) The replication defective recombinant adenovirus according to Claim 32, wherein the signal is a viral promoter.

34. (Twice Amended) The replication defective recombinant adenovirus according to Claim 33, wherein the signal is selected from the group consisting of an RSV-LTR promoter, an E1A promoter, an MLP promoter, and a CMV promoter.

35. (Twice Amended) A replication defective recombinant adenovirus comprising a cDNA encoding human prepro-BDNF, operably linked to an RSV-LTR promoter, wherein the adenovirus E1 gene is non-functional.

37. (Twice Amended) A replication defective recombinant adenovirus comprising a cDNA encoding human brain-derived neurotrophic factor (hBDNF) operably linked to a promoter controlling expression in a nerve cell, wherein the adenovirus E1 gene is non-functional.

38. (Twice Amended) The replication defective recombinant adenovirus according to Claim 37, wherein the promoter is selected from the group consisting of a neuron-specific enolase promoter and a GFAP promoter.

40. (Twice Amended) The replication defective recombinant adenovirus according to Claim 27, comprising ITRs and a sequence permitting encapsulation, wherein the E1 gene and at least one of the E2, E4 or L1-L5 genes are nonfunctional.

41. (Twice Amended) The replication defective recombinant adenovirus according to Claim 27, wherein the replication defective recombinant adenovirus is a type Ad 2 or Ad 5 human adenovirus or a CAV-2 type canine adenovirus.

42. (Twice Amended) A method for the treatment and/or prevention of a neurodegenerative disease comprising administration of an effective amount of the replication defective recombinant adenovirus according to Claim 27.

43. (Twice Amended) The method according to Claim 42, wherein the neurodegenerative disease is selected from the group consisting of Parkinson's disease, Alzheimer's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS).

44. (Twice Amended) A pharmaceutical composition comprising the replication defective recombinant adenovirus according to Claim 27 and a pharmaceutically acceptable vehicle.

45. (Amended) The pharmaceutical composition according to Claim 44, in injectable form.

46. (Twice Amended) The pharmaceutical composition according to Claim 44, comprising between 10^4 and 10^{14} pfu/ml of replication defective recombinant adenovirus.

47. (Twice Amended) The pharmaceutical composition according to Claim 46, comprising between 10^6 to 10^{10} pfu/ml of replication defective recombinant adenovirus.

48. (Twice Amended) A mammalian cell infected with the replication defective recombinant adenovirus according to Claim 27.

49. (Twice Amended) The mammalian cell according to Claim 48, wherein the mammalian cell is a human cell.

50. (Twice Amended) The mammalian cell according to Claim 49, wherein the mammalian cell is selected from the group consisting of a fibroblast, a myoblast, a hepatocyte, an endothelial cell, a glial cell, and a keratinocyte.

51. (Amended) An implant comprising a mammalian cell according to Claim 48 and an extracellular matrix.

52. (Twice Amended) The implant according to Claim 51, wherein the extracellular matrix comprises a gelling compound selected from the group consisting of collagen, gelatin, glucosaminoglycan, fibronectin, and lectin.

53. (Twice Amended) The implant according to Claim 51, wherein the extracellular matrix comprises a support permitting anchorage of the mammalian cell.

54. (Twice Amended) The implant according to Claim 53, wherein the support comprises a polytetrafluoroethylene fiber.